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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,561	11/11/2003	David A. Williams	7037-485	5476

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,561	WILLIAMS, DAVID A.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-5,8,9 and 16-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,8,9 and 16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/04/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 12/21/2006 in response to office action mailed on 05/23/2006 has been acknowledged.

Claims 1-2, 6-7 and 10-15 are cancelled

Claims 3, 5, 8, and 1-17 are amended.

Claims 3-5, 8-9 and 16-21 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recitation "mammal-human" or "mammal-human-1" makes the claim vague and indefinite. It is unclear what is "mammal-human-1" in this context.

Claim Rejections - 35 USC § 112

Claims *3-5, 8-9 and 16-21* are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of the claims in its breadth encompasses any viable cellular population infected with any retrovirus, use of any immobilized material that binds cells and retroviruses.

The specification provides guidance only to infection of cells with a retroviral vector that is of non-lentiviral origin and in the use of fibronectin as a material that binds retroviruses and cells (example 1). The specification does not disclose any other immobilized materials or ligands besides fibronectin that binds to cells and viruses. The application does not disclose sufficient umber of examples commensurate with the scope and breadth of instant claims. For example the specification as filed fails to disclose representative number of ligands that would specifically bind retrovirus and any kind of cells i.e., a ligand that specifically binds to retrovirus coat protein and a specific cell surface receptor.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (See In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. conserved motifs or domains, cell type characteristics etc).

Since the specification fails to disclose other claimed materials and engrafted cells, it is not possible to envision the broadly claimed compositions would provide the same results as single examples as mentioned above. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual

reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the instant case the compositions as claimed has been defined only by a statement of function that broadly encompasses all materials or ligands that bind a retrovirus and a cell and can be immobilized on a substrate which conveyed no distinguishing information about the identity of the broadly claimed species. Accordingly one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of a single member of this genus would not be representative of claimed genus of compounds and is insufficient to support the claim in its present scope.

Claims 5, 8-9 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification for the reason of record as set forth in the previous office action mailed on 05/23/2006.

In Response to Arguments of 12/21/2006**:**

Applicant amends claims for engrafting humans with a viable population of retrovirally transduced human cells. Applicant submits as declaration a prior art regarding human therapies carried out with retrovirally transduced cells particularly that of ADA-SCID (Blaese et al, 1995) and gene therapy of a patient with familial hypercholeterolaemia (Grossman et al, 1994) and further an article (with an after filing date) on gene therapy of XSCID (Hacein-Bey-Abina et al, 2002) to support his argument that gene therapy with retroviral transduced cells is enabled. However this is found not fully persuasive because the breadth of instant claim encompasses any engrafting or transplanting (autologous, allogenic etc) of any human cells (brain cells, kidney cells, cultured cells etc) transduced with any retrovirus (infectious, non-infectious, HIV virus, vector with a therapeutic gene etc) into any site in a human (brain, kidney, hematopoietic system etc) and via any route

of administration. Where as the specification provides by means of specific examples only guidance and/or evidences regarding transduction of hematopoietic progenitors and the engraftment of the said retroviral transduced mouse cells into a mouse by tail vein injection (example 7) and a long-term bone marrow reconstitution in mice (example 11). The specification thus fails to provide an enabling disclosure for the full scope and breadth of the invention as claimed. In the absence of adequate description of the enabled invention commensurate with the breadth and scope of the claim one of ordinary skill in the art would conclude that the claimed invention is unpredictable and would require an undue amount of experimentation to practice the full scope of the same. Provided the unpredictability of gene therapy, even encumbered with an art example provided by applicant (particularly X-SCID gene therapy) up on a later assessment of 'success' as indicated in office action mailed on 05/23/2006. Because of said unpredictability in the art, each different gene transfer methods and/or genetically engineered cell engraftments in humans for any intended therapy need to be assessed for enablement. Accordingly, in view of the unpredictability in the art of gene therapy and the lack of guidance provided by the specification with regard to an enabled use of methods for treating a human with said retroviral transduced cells as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of engrafting of retrovirus-transduced cells in non-human mammals. Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

Claims 3-4 and 16-17 are rejected under 35 USC 102 (b) as being anticipated by Williams et al., (1994, Blood Cells 20:504-516).

The above claims are directed to a viable cellular population transduced with retrovirus in presenece of a immobilized ligand and in a medium that is essentially free of hexadimethrine bromide wherein infection was performed without cocultivation with retroviral producer cells and and a method for cellular grafting in 'mammal-human' with said viable population of cells.

Regarding claims 3-4 Williams teaches a viable human umbilical cord blood stem cell population infected with retroviruses in the presence of fibronectin fragments that were immobilized on Petri dishes (p.504, Abstract, Fig.5) and the transfections were carried out without co-cultivation but with high efficiency using supernatant infection with ADA retroviral vector expressing PGK-mADA (p.509, 3rd paragraph bridging p.510). Williams is, silent about the use of hexadimethrine bromide in the medium but however, teaches that the above protocol is promising for gene delivery into human hematopoietic system. Thus the rejected claims are within the scope of William's disclosure.

Claim Rejections - 35 USC § 103

Claims 3-5, 8-9 and 16-21 rejected under 35 USC 103 (a) as being unpatentable over Moritz et al., (1994, The Journal of Clinical Investigation 93:1451-1457) and Nolta et al (1996, Proc. Natl. Acad. Sci. USA 93:2414-2419) in view of Papp et al., (1987 Biochim. Biophys. Acta 925:241-247) in view of amendments and cancellation of claims and further in view of a new rejection below.

Claims 3-5, 8-9 and 16-21 rejected under 35 USC 103 (a) as being unpatentable over Williams et al., (1994, Blood Cells 20:504-516) applied to claims 3-4 and 16-17 as above and further in view of Dunbar et al (1995, Blood 85:3048-3057) and Cornetta et al. (1989, J Virol Methods. 23:187-94).

The above claims are directed to a viable cellular population transduced with retrovirus in presenece of a immobilized ligand and in a medium that is essentially free of hexadimethrine bromide wherein infection was performed without co-cultivation with retroviral producer cells and a method for cellular grafting in 'mammal-human' with said viable population of cells.

Regarding claims 3-4 Williams teaches a viable human umbilical cord blood stem cell population infected with retroviruses in the presence of fibronectin fragments that were immobilized on Petri dishes (p.504, Abstract, Fig.5) and the transfections were carried out without co-cultivation but with high efficiency using supernatant infection with ADA retroviral vector expressing PGK-mADA (p.509, 3rd paragraph bridging p.510). Williams is, silent about the use of hexadimethrine bromide in the medium but however, teaches that the above protocol is promising for gene delivery into human hematopoietic system.

However, Williams does not explicitly teach grafting of retrovirally transduced cells into humns.

Regarding claims 5-9, 18-21 Dunbar teaches grafting or autologous transplantation into humans the retrovirally transduced CD34 enriched clinical grade hematopoietic cells (bone marrow or peripheral blood derived) that were infected using retroviral supernatant (in the absence of co-cultivation) in a medium that lacked hexadimethrine bromide (Abstract, p.3049, col.2, 3rd paragraphbridging p.3050).

Regarding limitation for not using polybrene (hexadiemthrine bromide) in the medium for retroviral transduction Cornetta teaches that protamine (5-10 ug/ml) in the transfection medium provided essentially the same infection efficiency as polybrene (hexadiemthrine bromide) and being relatively less toxic protamine is approved for human use by U. S. FDA. Thus protamine provided an effective alternative to polybrene (hexadiemthrine bromide) when developing human gene therapy protocols (Abstract).

Thus it would have been obvious for one of ordinary skill in the art to produce a retroviral transduced viable human cell population by an enhanced transduction without co-cultivation and involving the use of immobilized fibronectin as taught by Williams and using a culture medium that is essentially free polybrene (hexadimethrine bromide), as rationalized by Cornetta and graft the transduced cells into humans as taught by Dunbar. Further it would have been obvious for one of ordinary skill in the art to graft a viable pluripotent hematopoietic cells (stem cells) transduced with retrovirus under conditions as above into a human mammal as a part of gene therapeutic approach to treat certain genetically inherited diseases. One of ordinary skill in the art would be motivated to use the method of retroviral transduction of cells in the presence of immobilized fibronectin, without co-cultivation with virus producing cells and in a medium free of hexadimethrine bromide as it would enhance retrovirus transductions and facilitate safer and less toxic gene therapy of said diseases. One of ordinary skill in the art would have reasonable expectation of success of generating a desired retroviral-transduced cell population for gene therapy using the efficient transduction protocol that involved no co-cultivation with virus producing cells, because of the art teachings prior to instant invention. Thus, the claimed invention was *prima facie* obvious.

Double Patenting

Claims 3 and 4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 19 of U.S. Patent No. 6,670,177 B2 for the reason of record as set forth in the previous office action mailed on 05/23/2006.

In Response to Arguments of 12/21/2006**:**

Applicant argues that double patenting rejection be held in abeyance until a final decision is made regarding other rejections in the instant prosecution. However this was found not persuasive and hence the rejection is maintained.

Claims 3 and 4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-22 of U.S. Patent No. 5,686,278 for the reason of record as set forth in the previous office action mailed on 05/23/2006.

In Response to Arguments of 12/21/2006**:**

Applicant argues that double patenting rejection be held in abeyance until a final decision is made regarding other rejections in the instant prosecution. However this was found not persuasive and hence the rejection is maintained.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public

only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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